THE JOURNAL OF Organic Chemistry®

Volume 21, Number 9

October 16, 1956

[FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

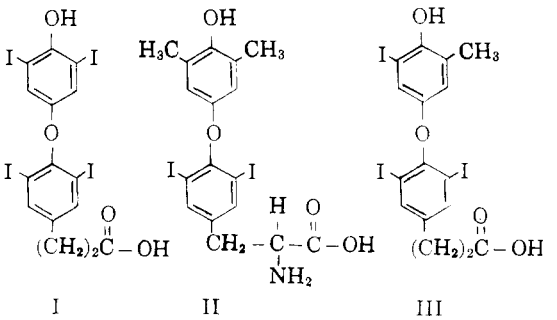
The Synthesis of Some Methyl Analogs of Desaminothyroxine[1]

NORMAN KHARASCH, SARKIS H. KALFAYAN, AND J. DOUGLAS ARTERBERRY

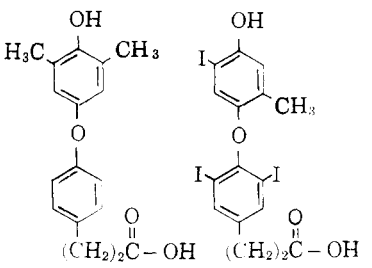
Received March 5, 1956

Studies of desaminothyroxine (I) and its derivatives, which are of potential physiological interest, have been extended. Modifications in the preparation of I are described and the syntheses of three methyl analogs of I are reported, namely: 3,5-diiodo-4-(4′-hydroxy-5′-iodo-3′-methylphenoxy)hydrocinnamic acid, 3,5-diiodo-4-(4′-hydroxy-5′-iodo-2′-methylphenoxy)hydrocinnamic acid, and 3,5-diiodo-4-(3′,5′-dimethyl-4′-hydroxyphenoxy)hydrocinnamic acid. Numerous new intermediates required for the preparation of the above compounds are also recorded.

In a previous study from this Laboratory, Bruice, Winzler, and Kharasch[2] reported that desaminothyroxine (I) has remarkably high activity (about 130 times that of D,L-thyroxine) on tadpole metamorphosis, and that the 3′,5′-dimethyl analogs (II) of L and D,L-thyroxine have higher activities (in the same test) than the thyroxines themselves.[3] As a logical extension of these observations, and especially in view of the empirical correlation between thyroxine-like activities and structure proposed by Bruice, Kharasch, and Winzler,[4] it is now desirable to know the biological activities of selected methyl analogs of desaminothyroxine, such as III, IV, and V. This paper reports the syntheses of these substances, as well as useful modifications in the preparation of desaminothyroxine (I), which may also be designated as "thyropropionic acid," and whose synthesis has been previously reported.[5]



I II III



IV V

The methyl analogs of I, as well as I itself, were synthesized by condensing the appropriate *p*-methoxyphenol with X, whose synthesis was conveniently attained by the following sequence:

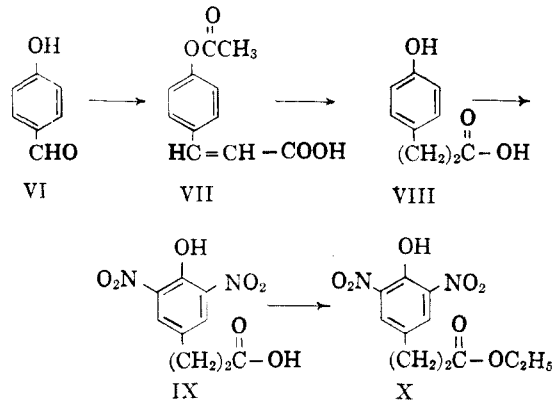
(1) This investigation was supported, in part, by research grant A-703 of the National Institutes of Health, Public Health Service.

(2) Bruice, Winzler, and Kharasch, *J. Biol. Chem.*, 210, 1 (1954).

(3) Selenkow and Asper, *Physiol. Revs.*, **35**, 454 (1955), reported that I is about 1/4 to 1/5 as active as L-thyroxine in the rat goiter-prevention assay. Roche, Michel, Wolf, and Etling, *Compt. rend. soc. biol.*, **148**, 1738 (1954), reported that I had 75% the activity of D,L-thyroxine in the rat goiter-prevention assay, while the tri-iodo analog was as active as D,L-thyroxine. Roth (*Compt. rend. soc. biol.*, **149**, 1180 (1955), found I to be 1000 times as active as D,L-thyroxine and about 100 times as active as L-tri-iodothyronine in the *Rana catesbeiana* test (*Cf.* Ref. 2). For a discussion of the possible relation between amphibian and mammalian response to thyroxine and its analogs, *Cf.* Ref. 4.

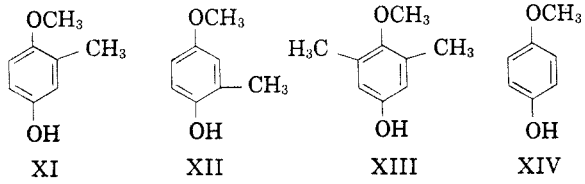
(4) Bruice, Kharasch, and Winzler, *Archives of Biochemistry and Biophysics*, **62**, 305–314 (1956).

(5) (a) Clayton, Green, and Hems, *J. Chem. Soc.*, 2467 (1951). (b) Bruice, *J. Org. Chem.*, **19**, 333 (1954), for modifications in the synthesis of ethyl 3,5-dinitrophloretic acid, a precursor in the synthesis of I.

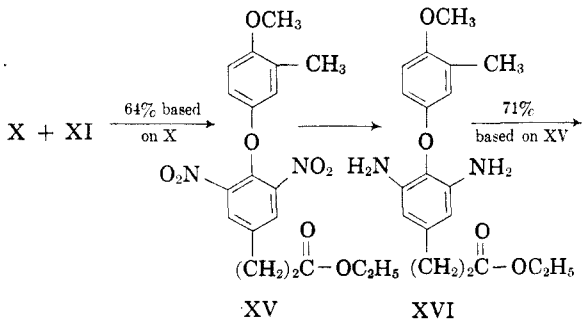


Intermediate VII was not isolated from the Perkin reaction of VI, but was reduced directly to phloretic acid, VIII, using Raney nickel in aqueous alkali.

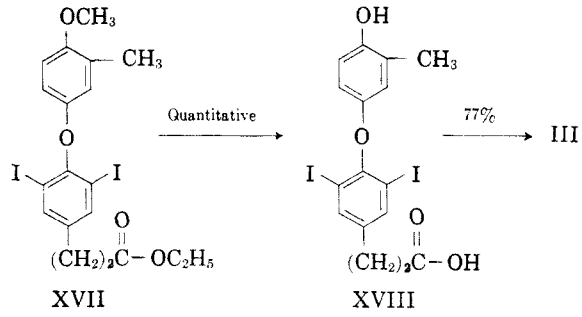
The Elbs persulfate oxidation, as adapted by Baker and Brown,[6] has been generally used to synthesize the phenolic precursors, XI, XII, and XIII. While XIII was thus prepared, using the conveniently soluble ammonium persulfate, as suggested by Barnes, *et al.*,[7] XI and XII were obtained much more conveniently by methylating *p*-toluhydroquinone. In this procedure, XI and XII are formed simultaneously and can be easily separated. This modification avoids the low yields and tedious aspects of the Baker and Brown method for XI, and provides XII at the same time, as well. Compound XIV is available commercially.



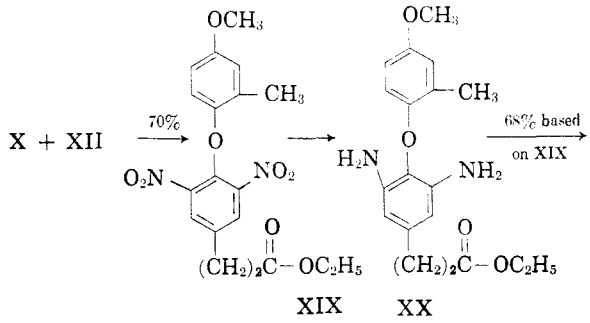
The general method of Ullman and Nadai,[8] as adapted by Burrows, *et al.*[9] was used to condense the "halves," such as X and XI, to give the diphenyl ethers. The pyridinium tosylate intermediate was not isolated in any case. The synthetic sequences for III, V, IV and I are shown below.

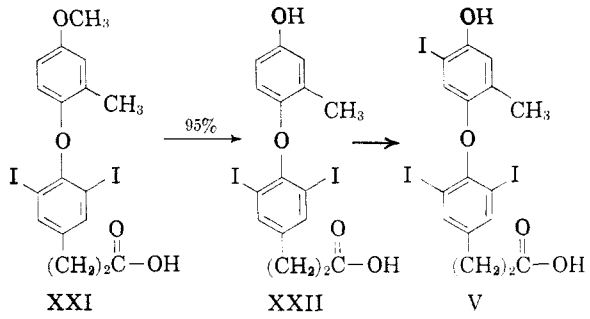


(6) Baker and Brown, *J. Chem. Soc.*, 2303 (1948).
(7) Barnes, Cookson, Dickson, Elks, and Poole, *J. Chem. Soc.*, 1448 (1953).
(8) Ullman and Nadai, *Ber.*, 41, 1872 (1908).
(9) Burrows, Clayton, Hems, and Long, *J. Chem. Soc.*, S 190 (1949).

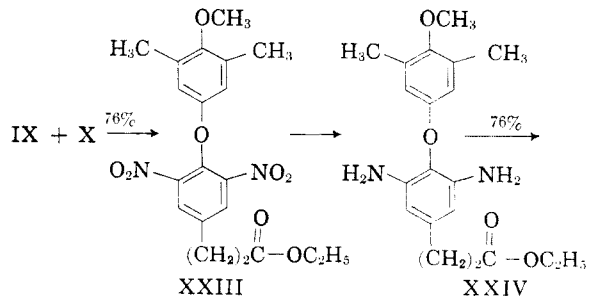


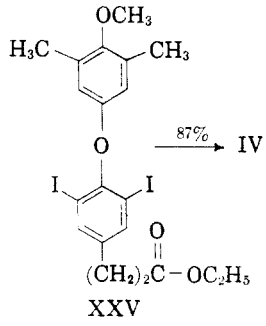
XV was converted to XVII without isolating XVI. The sequence for V was:





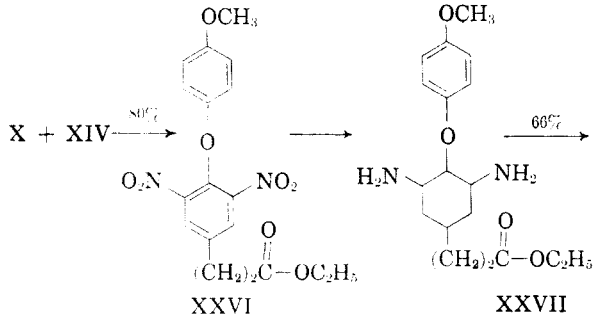
Although a large excess of iodine was used in the last step, only one iodine atom was introduced into the prime ring. We have assigned the iodine to position 5′, since this is *para* to the methyl and *ortho* to the hydroxyl substituent and would be expected to be more susceptible to substitution than position 3′. Compound IV was obtained as follows:



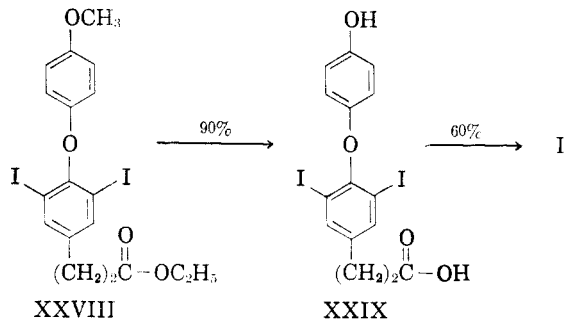


XXV

The steps which led to I were:



XXVI XXVII



XXVIII XXIX

EXPERIMENTAL[10]

ETHYL 3,5-DINITRO-4-HYDROXYHYDROCINNAMATE (X)

p-Hydroxyhydrocinnamic acid (phloretic acid), VIII. *p*-Hydroxybenzaldehyde (40 g., 0.33 mole), freshly fused and powdered sodium acetate (64 g., 0.78 mole), and acetic anhydride (100 ml.) were refluxed 24 hous. The mixture was cooled to 100° and poured into one liter of 15% sodium hydroxide solution. Raney nickel (69 g.) was added to the resulting red solution during 3–4 hours, keeping the temperature at 65–75°. After complete addition, the mixture was again heated for 2 hours on the steam-bath. Charcoal (5 g.) was added and the mixture was stirred, filtered through sintered glass, acidified (Congo red indicator) with hydrochloric acid, cooled, and extracted with ether. The semi-solid residue, obtained after removing the ether, was distilled (155–165°; 1–2 mm.) to give the crude phloretic acid. Recrystallization from a mixture of benzene and petroleum ether (b.p., 88–99°) gave 21 g. of the acid (VIII), m.p. 129–130°. To obtain IX, 27.8 g. of VIII was nitrated[5b] to give 34 g. (80%) of the product (m.p. 135–136°). X was obtained in 85% yield,[5] m.p. 73–74° after precipitation from chloroform solution by addition of petroleum ether (b.p. 88–98°).

(10) Melting points were taken on a Fischer-Johns block. The microanalyses were carried out by Mr. W. J. Schenck.

4-METHOXY-3-METHYLPHENOL (XI), 4-METHOXY-2-METHYLPHENOL (XII) AND 3,5-DIMETHYL-4-METHOXYPHENOL (XIII)

To a stirred solution of *p*-toluhydroquinone (62.5 g., 0.5 mole) in sodium hydroxide (50 g., 1.25 moles) and water (350 ml.), chilled to 10°, methyl sulfate (75.6 g., 0.6 mole) was added in portions, keeping the temperature at 10°. After complete addition, the mixture was stirred one more hour and extracted with ether, to remove any dimethylated hydroquinone. The aqueous layer was made strongly acidic with hydrochloric acid, and extracted with ether. Solvent was aspirated from the extract and the oily residue was distilled, first at water-pump pressure, then at atmospheric pressure. The fraction boiling at 240–250° (1 atm.) consisted of *ca.* 50 g. and was cooled to 10°, giving crystals of 4-methoxy-2-methylphenol (XII). Repeated cooling of the distillate and collection of successive crops of crystals gave a total of 24 g. (37.6%) of product, m.p. 71–72° (Lit.[6] reports m.p. 70.5–71.5° after recrystallization from water). The filtrate consisting mainly of XI, was redistilled, and the fraction boiling at 240–245° (1 atm.) was collected. Yield, 21 g.; 35%. Attempts to recrystallize this isomer from benzene–petroleum ether failed; but on standing in an open flask for several days it solidified (m.p. 44°). The reported value[6] is 45–46°. Compound XI was also prepared by the Elbs reaction,[6] but the yields were only 10–15% and the preparation much more tedious.

Compound XIII was prepared by means of the Elbs persulfate oxidation on 2,6-dimethylphenol (Eastman) as directed by Baker and Brown,[6] and methylating the intermediate sulfate.

3,5-DIIODO-4-(4′-HYDROXY-5′-IODO-3′-METHYLPHENOXY)-HYDROCINNAMIC ACID (III)

Ethyl 3,5-dinitro-4-(4′-methoxy-3′-methylphenoxy)hydrocinnamate (XV). Compound X (4.0 g., 0.014 mole), *p*-toluenesulfonyl chloride (2.7 g., 0.014 mole), and dry pyridine (100 ml.) were heated (steam-bath) under dry conditions, for 10 min. Compound XI (7.7 g., 0.056 mole) was added and the mixture was refluxed one hour. Aspiration of the solvent left a gum, which was dissolved in alcohol (85 ml., 70%), and the solution was treated with charcoal, then cooled and filtered, giving 3.6 g. (64%) of product. The m.p., after recrystallizing from alcohol was 75–76°.

Anal. Calc'd for $C_{19}H_{20}N_2O_8$ (XV): C, 56.43; H, 4.95; N, 6.93. Found: C, 56.87; H, 4.73; N, 6.89.

3,5-Diiodo-4-(4′-hydroxy-3′-methylphenoxy)hydrocinnamic acid (XVIII). Compound XV (2.1 g., 0.0052 mole) in acetic acid (100 ml.) was hydrogenated (room temp., 25 p.s.i.) over palladized-charcoal (10%, 0.5 g.). The hydrogenation mixture was filtered and added, dropwise, during 45 min. to a stirred solution of sodium nitrite (2.2 g.) in a sulfuric acid–acetic acid mixture (80 ml. of each), at −5°. After stirring one more hour, the solution of the diazotized diamine was added fairly rapidly to a vigorously stirred solution of iodine (7 g.), sodium iodide (10 g.), and urea (1 g.) in water (300 ml.), which was underlaid with 100 ml. of chloroform. No attempt to cool the mixture was made during the addition, and the temperature rose to 35°. After stirring 2 hours, the chloroform layer was separated, the aqueous layer was extracted with chloroform, and the combined extracts were shaken with aqueous sodium bisulfite solution. After washing the chloroform layer with water and aspirating the solvent a gum remained. This was dissolved in 60 ml. of benzene and chromatographed on an alumina column, using a 10% solution of methanol in benzene as eluent. The ester, XVII, was obtained from the eluate in 71% yield (2.05 g.) and melted at 85–86° after recrystallization from absolute alcohol. The product was converted directly to the acid, XVIII.

Conversion of XVII to XVIII. The ester XVII (2 g.) was refluxed with 20 ml. of a 1:1 mixture of acetic acid and

47% hydriodic acid. A quantitative yield of XVIII (white crystals) was obtained on cooling the reaction mixture and diluting it with water. The acid melted at 195–196°, after recrystallizing from 95% ethanol.

Anal. Calc'd for $C_{16}H_{14}I_2O_4$ (XVIII): C, 36.64; H, 2.67; I, 48.44. Found: C, 37.42; H, 2.68; I, 48.28.

Conversion of XVIII to III. One gram of XVIII was dissolved in 25 ml. of 25% aqueous methylamine. The temperature was kept below 20° while 2.5 ml. of 2 *N* iodine in potassium iodide was added, during 15 min. The mixture was stirred one hour, acidified with 15% hydrochloric acid, and the precipitated III was collected, repeatedly dissolved in aqueous ammonia, and reprecipitated by adding hydrochloric acid, then recrystallized from 70% ethanol. The yield was 0.95 g. (77%); m.p. 184–188°.

Anal. Calc'd for $C_{16}H_{12}I_3O_4$ (III): C, 29.57; H, 2.00; I, 58.71. Found: C, 30.46; H, 2.38; I, 59.7.

3,5-DIIODO-4-(4'-HYDROXY-2'-METHYLPHENOXY)HYDROCINNAMIC ACID (XXII) AND 3,5-DIIODO-4-(4'-HYDROXY-5'-IODO-2'-METHYLPHENOXY)HYDROCINNAMIC ACID (V)

Ethyl 3,5-dinitro-4-(4'-methoxy-2'-methylphenoxy)hydrocinnamic acid (XIX). This substance was obtained from X plus XII, by the same procedure as was used to prepare XV from (X plus XI). Yield, 4.0 g. 70%; m.p. 97–98°.

Anal. Calc'd for $C_{19}H_{20}N_2O_8$ (XIX): C, 56.4; H, 4.95; N, 6.93. Found: C, 56.20; H, 4.68; N, 6.80.

Ethyl 3,5-diiodo-4-(4'-methoxy-2'-methylphenoxy)hydrocinnamate (XXI). The procedure used for synthesis of XVII was adopted for converting XIX to XXI, with the minor change of using 5% palladized charcoal instead of the usual 10%. The product was obtained in 68% yield, and melted at 121–122°. From 3.6 g. of XIX, there was obtained 3.4 g. (68%) of XXI.

Anal. Calc'd for $C_{19}H_{20}I_2O_4$: C, 40.29; H, 3.53; I, 44.84. Found: C, 40.07; H, 3.58; I, 44.92.

3,5-Diiodo-4-(4'-hydroxy-2'-methylphenoxy)hydrocinnamic acid (XXII). Ester XXI (3.0 g. was refluxed with a mixture of acetic acid (20 ml.) and hydriodic acid (15 ml., 47%) for two hours. White crystals began to separate even before refluxing was stopped. The mixture was cooled and the product was collected and washed with water. Yield, 2.7 g. (95%); m.p. 228–229°, after recrystallization from 95% ethanol.

Anal. Calc'd for $C_{16}H_{14}I_2O_4$ (XXII): C, 36.71; H, 2.68; I, 48.44. Found: C, 37.00; H, 2.93; I, 47.20.

Conversion of XXII to V. One-half gram of XXII was dissolved in 20 ml. of 33% ethylamine and a solution of iodine in potassium iodide (1.8 ml. of 1.9 *N*) was added during 15 min. The mixture was stirred one hour and acidified with 15% hydrochloric acid. The precipitated V was collected and repeatedly dissolved in 1 *N* sodium hydroxide and reprecipitated by adding hydrochloric acid. After washing and drying, buff-colored, minute crystals were obtained. Yield 0.55 g. (74%); m.p. 179–184°.

Anal. Calc'd for $C_{16}H_{13}I_3O_4$: C, 29.57; H, 2.00; I, 58.71. Found: C, 30.89; H, 2.67; I, 58.53; 59.13 (on different samples).

3,5-DIIODO-4-(3',5'-DIMETHYL-4-HYDROXYPHENOXY)HYDROCINNAMIC ACID (IV)

Ethyl 3,5-dinitro-4-(3',5'-dimethyl-4'-methoxyphenoxy)hydrocinnamate (XXIII). Condensation of IX and XI, by the method used to prepare XV, gave XXIII in 76% yield; m.p. 115–116°, after recrystallization from alcohol.

Anal. Calc'd for $C_{20}H_{22}N_2O_8$ (XXIII): C, 57.42; H, 5.26; N, 6.70. Found: C, 57.38; H, 5.26; N, 6.59.

Ethyl 3,5-diiodo-4-(3',5'-dimethyl-4'-methoxyphenoxy)hydrocinnamate (XXV). Compound XXIII was reduced, the diamine was diazotized, and iodinated, as in the preparation of XVIII, to give this diiodo ester, in 76% yield; m.p. 84°.

Anal. Calc'd for $C_{20}H_{22}I_2O_4$ (XXV): C, 41.37; H, 3.79; I, 43.75. Found: C, 41.05; H, 3.41; I, 44.00.

3,5-Diiodo-4-(3',5'-dimethyl-4'-hydroxyphenoxy)hydrocinnamic acid (IV). Compound XXV (3.1 g.) was refluxed with a mixture of acetic acid (30 ml.) and hydriodic acid (25 ml. of 47%) for 3 hours. On cooling, white crystals deposited and were collected. Addition of water to the filtrate yielded a further crop of product. Total yield: 2.5 g. (87%); m.p. 217–219°.

Anal. Calc'd for $C_{17}H_{16}I_2O_4$: C, 37.92; H, 2.97; I, 47.2. Found: C, 38.30; H, 2.91; I, 47.68.

DESAMINOTHYROXINE (I)

Compound X (5.0 g., 0.017 mole), *p*-toluenesulfonyl chloride (3.35 g., 0.017 mole), and dry pyridine (80 ml.) were heated on the steam-bath for 15 minutes, under dry conditions. Compound XIV (9.0 g., 0.072 mole) was added and the mixture was refluxed one hour. The solvent was aspirated and the resulting gum was recrystallized from absolute alcohol (85 ml.), giving 5.6 g. (80%) of *ethyl 3,5-dinitro-4-(4'-methoxyphenoxy)hydrocinnamate*, XXVI; yellow crystals, m.p. 102–103°. The latter product was reduced, and the diamine was diazotized and iodinated (as described for XVII) to give *ethyl 3,5-diiodo-4-(4'-methoxyphenoxy)hydrocinnamate*, XXVIII, in 66% yield. M.p. 76°, after recrystallization from aqueous ethanol. XXVIII then was demethylated and deesterified, by refluxing two hours with 20 ml. of a 1:1 mixture of acetic acid and hydriodic acid (47%). On cooling, white crystals deposited. These turned a slight buff color on standing. Yield: 1.5 g (90%); m.p. 248–249°, of *3,5-diiodo-4-(4'-hydroxyphenoxy)hydrocinnamic acid* (XXIX). The reported m.p. is 250°.

Compound XXIX (1.50 g.), in 40 ml. of aqueous 25% methylamine was stirred, while a solution of iodine in sodium iodide (2 *N*, 2.8 ml.) was added dropwise during 0.5 hour, keeping the temperature below 10°. At the end of the addition, the separation of a white solid was noticed. After stirring one hour more, the solution was acidified with 15% hydrochloric acid, and the precipitated product was recrystallized from aqueous acetone, yielding minute brownish crystals, m.p. 170–180°. Treatment with charcoal and several recrystallizations from aqueous acetone gave a white product. Yield: 1.30 g. (60%); m.p. 213–215°. The reported value[5] is 218–222°.

Anal. Calc'd for $C_{15}H_{10}I_4O_4$: C, 23.65; H, 1.31; I, 66.62. Found: C, 23.78; H, 1.53; I, 66.31.

UNIVERSITY PARK, LOS ANGELES 7, CALIFORNIA